# (19) World Intellectual Property Organization

International Bureau



(43) International Publication Date 31 December 2003 (31.12.2003)

PCT

(10) International Publication Number WO 2004/000315 A1

A61K 31/44. (51) International Patent Classification<sup>7</sup>: 31/192, A61P 9/10, 3/10, 3/06, C07C 323/20, C07D 213/30, 213/32, C07C 59/66, 59/68, C07D 213/34

(21) International Application Number:

PCT/EP2003/006415

(22) International Filing Date: 18 June 2003 (18.06.2003)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data: 0214149.7

19 June 2002 (19.06.2002)

(71) Applicant (for all designated States except US): **CORPORATION** SMITHKLINE **BEECHAM** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(71) Applicant and

(72) Inventor: HAMLETT, Christopher, Charles, Frederick [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): BELL, Richard [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). BESWICK, Paul, John [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB). GOSMINI, Romain, Luc, Marie [FR/FR]; Laboratoire Glaxo-SmithKline, Centre de Recherches, Z.A. de Courtaboeuf,

25, avenue du Quebec, F-91940 Les Ulis (FR). KING, Nigel, Paul [GB/GB]; GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW (GB). PATEL, Vipulkumar, Kantibhai [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: LEAROYD, Stephanie, Anne; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

### Published:

with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENYLALKANOIC ACID AND PHENYLOXYALKANOIC ACID DERIVATIVES AS HPPAR ACTIVATORS

HO 
$$R^1$$
  $R^2$   $R^3$   $R^5$   $R^6$   $R^7$ 

(57) Abstract: The present invention provides a compound of formula (I):wherein:R1 and R2 are independently H or C1-3 alkyl; X represents a O or (CH2)n where n is 0, 1 or 2;R3and R4 independently represent H, C1-3 alkyl, -OCH3, -CF3, allyl, or halogen;X1 represents O, S, SO2, SO, or CH2;R5 and R6 independently represent hydrogen, C1-6 alkyl (including branched alkyl and optionally substituted by one or more halogens or C1-6alkoxy), or together with the carbon atom to which they are bonded form a 3-6 membered cycloalkyl ring;R7 represents a phenyl or a 6 membered heteroaryl group containing 1, 2 or 3 nitrogen atoms wherein the phenyl or heteroaryl group is substituted by 1, 2 or 3

moieties selected from the group consisting of halogen, C1-6 alkoxy, C1-6 alkyl, CF3, hydroxy, or phenyl (which may be optionally substituted by one or more C1-3 alkyl, -OC1-3 alkyl, CN, acetyl, hydroxy, halogen or CF3).



onal Application No PCT/EP 03/06415

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61K31/192

CO7D213/34

C07C323/20

A61P9/10 CO7D213/32 CO7D213/30

A61P3/10 C07C59/66 A61P3/06 C07C59/68

According to International Patent Classification (IPC) or to both national classification and IPC

Minimum documentation searched (classification system followed by classification symbols)  $IPC\ 7\ CO7C\ CO7D\ A61K$ 

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data, PAJ

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
х	WO 99 11255 A (ONO PHARMACEUTICAL CO., LTD., JAPAN) 11 March 1999 (1999-03-11) see compounds 26-157, 26-158 page 200; table 26 see componds 26-196 and 26-197 page 201; table 27 page 192 see compounds 26-299 - 26-302 page 204	1-21
X	WO 00 64876 A (MCGEEHAN GERARD M ; MORRIS ROBERT (US); ZHANG LITAO (US); BOBKO MAR) 2 November 2000 (2000-11-02) claims 1,50-88	1-21
A	EP 1 067 109 A (ONO PHARMACEUTICAL CO) 10 January 2001 (2001-01-10) the whole document	1-21

Further documents are listed in the continuation of box C.	X Patent family members are listed in annex.		
Special categories of cited documents:      A' document defining the general state of the art which is not considered to be of particular relevance      E' earlier document but published on or after the international filing date      L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)      O' document referring to an oral disclosure, use, exhibition or other means      P' document published prior to the international filing date but later than the priority date claimed	T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  "&" document member of the same patent family		
Date of the actual completion of the international search  26 September 2003	Date of mailing of the international search report  10/10/2003		
Name and mailing address of the ISA  European Patent Office, P.B. 5818 Patentiaan 2  NL - 2280 HV Rijswijk  Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  Fax: (+31-70) 340-3016	Authorized officer  Schmid, J-C		





	PCI/EP 03/06415
ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
WO 97 31907 A (CALLAGHAN JOHN MARK O;GLAXO GROUP LTD (GB); COBB JEFFREY EDMOND () 4 September 1997 (1997-09-04) the whole document	1-21
EP 1 132 376 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 September 2001 (2001-09-12) see formula (IV) page 18, line 1-9 page 37, line 1-24	1,13
GENTLES, ROBERT G. ET AL: "Standardization Protocols and Optimized Precursor Sets for the Efficient Application of Automated Parallel Synthesis to Lead Optimization: A Mitsunobu Example" JOURNAL OF COMBINATORIAL CHEMISTRY (2002), 4(5), 442-456, XP002255800 page 454, left-hand column	1,13
EP 1 283 039 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 February 2003 (2003-02-12) page 27; example 4 see formula (IV)	1,13
& WO 01 087293 A 22 November 2001 (2001-11-22)	1,13
WO 01 36351 A (LEWIS RONALD D II ;CORVAS INT INC (US); DUNCAN DAVID F (US); MADIS) 25 May 2001 (2001-05-25) claims; figures 1H,1J,2K,,2L,2V; examples 3,4	1-12
KUCHAR M ET AL: "BENZYLOXYARYLALIPHATIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 47, 1982, pages 2514-2524, XP001002034 ISSN: 0010-0765 examples	1-12
	WO 97 31907 A (CALLAGHAN JOHN MARK O;GLAXO GROUP LTD (GB); COBB JEFFREY EDMOND () 4 September 1997 (1997-09-04) the whole document  EP 1 132 376 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 September 2001 (2001-09-12) see formula (IV) page 18, line 1-9 page 37, line 1-24  GENTLES, ROBERT G. ET AL: "Standardization Protocols and Optimized Precursor Sets for the Efficient Application of Automated Parallel Synthesis to Lead Optimization: A Mitsunobu Example" JOURNAL OF COMBINATORIAL CHEMISTRY (2002), 4(5), 442-456, XP002255800 page 454, left-hand column  EP 1 283 039 A (TAKEDA CHEMICAL INDUSTRIES, LTD., JAPAN) 12 February 2003 (2003-02-12) page 27; example 4 see formula (IV) page 21, line 5 & WO 01 087293 A 22 November 2001 (2001-11-22)  WO 01 36351 A (LEWIS RONALD D II; CORVAS INT INC (US); DUNCAN DAVID F (US); MADIS) 25 May 2001 (2001-05-25) claims; figures 1H,1J,2K,,2L,2V; examples 3,4  KUCHAR M ET AL: "BENZYLOXYARYLALIPHATIC ACIDS: SYNTHESIS AND QUANTITATIVE RELATIONS BETWEEN STRUCTURE AND ANTIINFLAMMATORY ACTIVITY" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 47, 1982, pages 2514-2524, XP001002034 ISSN: 0010-0765

1



Intermonal Application No PCT/EP 03/06415

		FC1/EF 03/00415		
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT  Category • Citation of document, with indication,where appropriate, of the relevant passages Relevant to claim				
Category *	Giation of document, with indication, where appropriate, of the relevant passages	He	novani io stanii 140.	
X	KUCHAR M ET AL: "THE EFFECTS OF LIPOPHILICITY ON THE INHIBITION OF DENATURATION OF SERUM ALBUMIN AND ON THE ACTIVATION OF FIBRINOLYSIS OBSERVED WITH ASERIES OF BENZYLOXYARYLALIPHATIC ACIDS" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, ACADEMIC PRESS, LONDON, GB, vol. 48, 1983, pages 1077-1088, XP001002033 ISSN: 0010-0765 examples		1-12	
X	examples US 4 221 919 A (GRIMOVA JAROSLAVA ET AL) 9 September 1980 (1980-09-09) examples		1-12	

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, a meaningful search over the whole breadth of the claim(s) is impossible. Consequently, the search has been restricted to claim 13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



## INTERNATIONAL SEARCH REPORT

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Although claims 20 and 21 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X	Claims Nos.:  because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
	see FURTHER INFORMATION sheet PCT/ISA/210
з. 🔲	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	ernational Searching Authority found multiple inventions in this international application, as follows:
!	
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
	<b>,</b>
з. 🗌	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report Is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
	·
Remari	k on Protest  The additional search fees were accompanied by the applicant's protest.
	No protest accompanied the payment of additional search fees.
i	



Information on patent family members

Intermional Application No PCT/EP 03/06415

				FCI/Er	03/00415
Patent document cited in search report	:	Publication date		Patent family member(s)	Publication date
WO 9911255	Α	11-03-1999	AU WO	8750298 A 9911255 A1	22-03-1999 11-03-1999
WO 0064876	Α	02-11-2000	AU	4807000 A	10-11-2000
	••	<u> </u>	BR	0010126 A	26-02-2002
			CA	2371308 A1	02-11-2000
			CN	1356983 T	03-07-2002
			CZ	20013834 A3	17-04-2002
			EE	200100558 A	16-12-2002
			EΡ	1177176 A1	06-02-2002
			HR	20010793 A1	28-02-2003
			HU	0200997 A2	29-07-2002
		C C	JP	2002543065 T	17-12-2002
		J	NO	20015226 A	05-12-2001
			PL	351470 A1	22-04-2003
			SK	15522001 A3	04-06-2002
			WO	0064876 A1	02-11-2000
			_ZA 	200108800 A	10-02-2003
EP 1067109	Α	10-01-2001	AU	3275999 A	27-09-1999
			EP	1067109 A1	10-01-2001
			US	6506757 B1 9946232 A1	14-01-2003 16-09-1999
			WO US	2003153579 A1	14-08-2003
WO 9731907	Α	04-09-1997	AP	780 A	22-11-1999
			AT	205485 T	15-09-2001
			AU AU	717699 B2	30-03-2000 16-09-1997
			BG	2093597 A 102792 A	31-08-1999
			BR	9707786 A	27-07-1999
			CA	2247443 A1	04-09-1997
			CN	1218460 A ,B	02-06-1999
			CZ	9802750 A3	13-01-1999
			DE	69706658 D1	18-10-2001
			DE	69706658 T2	20-06-2002
			DK	888317 T3	21-01-2002
			EΑ	1403 B1	26-02-2001
			ΕE	9800288 A	15-02-1999
			MO	9731907 A1	04-09-1997
			EP	0888317 A1	07-01-1999
			ES HK	2163125 T3 1015369 A1	16-01-2002 15-02-2002
			HR	970110 A1	30-04-1998
			HU	0004845 A2	28-05-2001
			ΪL	125796 A	14-06-2001
			ĴΡ	3255930 B2	12-02-2002
			JΡ	2000507216 T	13-06-2000
			NO	983940 A	27-10-1998
			NZ	331381 A	23-06-2000
			PL	328871 A1	01-03-1999
			PT	888317 T	28-03-2002
			SI	888317 T1	30-04-2002
			SK	116398 A3	13-04-1999
			TR	9801707 T2	21-12-1998
			US ZA	6294580 B1 9701645 A	25-09-2001 10-12-1997
			4H 	9/UI045 A	10-12-133/
				<del></del>	



Internation No PCT/EP 03/06415

information on patent family members

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
EP 1132376 A	12-09-2001	AU CA EP US WO JP	1183300 A 2351692 A1 1132376 A1 6586475 B1 0031021 A1 2000212076 A	13-06-2000 02-06-2000 12-09-2001 01-07-2003 02-06-2000 02-08-2000
EP 1283039 A	12-02-2003	AU CA EP CN WO JP	5877101 A 2407088 A1 1283039 A1 1438883 T 0187293 A1 2002037731 A	26-11-2001 22-11-2001 12-02-2003 27-08-2003 22-11-2001 06-02-2002
WO 0136351 A	25-05-2001	AU WO	1624801 A 0136351 A2	30-05-2001 25-05-2001
US 4221919 A	09-09-1980	CS AT AT BE CA CH DE DK FI FR GB JP NL SE	175831 B1 341506 B 953075 A 836679 A1 1074330 A1 619205 A5 2556474 A1 573475 A ,B, 753551 A ,B, 2294689 A1 1487149 A 51086442 A 7514725 A 427108 B 7514212 A	31-05-1977 10-02-1978 15-06-1977 16-04-1976 25-03-1980 15-09-1980 01-07-1976 18-06-1976 18-06-1976 28-09-1977 29-07-1976 21-06-1976 07-03-1983 18-06-1976